

ISMP Adverse Drug Reactions

***Pneumocystis jiroveci* Pneumonia in an Infant Treated with Oral Steroids**

All-Trans Retinoic Acid as a Cause of Respiratory Failure

Dronabinol-Induced Gynecomastia

Neutrophilic Dermatitis Seen With Bortezomib

Unfavorable Smell With a Selective Serotonin Reuptake Inhibitor

Aloe Vera-Induced Hepatitis

Pulmonary Sarcoidosis Attributed to Etanercept

Serious Adverse Drug Events Reported to the Food and Drug Administration

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the Food and Drug Administration's (FDA) MEDWATCH program (800-FDA-1088). If you have reported an interesting preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Shuster at ISMP, 1800 Byberry Road, Suite 810, Huntingdon Valley, PA 19006 (phone: 215-947-7797; fax: 215-914-1492; e-mail: joel.shuster@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices in cooperation with the FDA's MEDWATCH Program and Temple University School of Pharmacy. ISMP is an FDA MEDWATCH partner.

***PNEUMOCYSTIS JIROVECI* PNEUMONIA IN AN INFANT TREATED WITH ORAL STEROIDS**

A 2-month-old girl was born with a large facial hemangioma

just under her lower lip. These benign tumors are common in infancy and are considered self-limiting. Because up to 30% of hemangiomas in children cause

some type of complication, it was decided that the young girl be treated with high-dose corticosteroids. There are no approved drugs to treat hemangiomas; how-

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ever, corticosteroids have been used in this fashion since the 1960s.

The child was given 15 mg of oral prednisolone daily starting at 2 months of age. When attempts were made to wean the child from the steroid, the hemangioma started to grow. She remained on prednisolone 15 mg daily until at 7 months of age, when she developed severe respiratory difficulty, fever, grunting, intercostal retractions, and lung infiltrates on chest x-ray. The complications advanced to the point that she had to be placed on a ventilator. Culture of the endotracheal aspirates revealed the presence of *Pneumocystis jiroveci* pneumonia. She responded well to intravenous (IV) therapy with trimethoprim/sulfamethoxazole while being intubated for a total of 10 days. She was discharged home on day 15 of hospitalization on a tapering dose of prednisolone and twice-weekly oral trimethoprim/sulfamethoxazole prophylaxis.

The authors report that 1 other similar case is in the literature, where a 2-month-old developed *Pneumocystis* pneumonia after 5 weeks of prednisone therapy. They state that *Pneumocystis* prophylaxis with trimethoprim/sulfamethoxazole should be considered in any child being placed on long-term corticosteroid therapy.

(Editor's note: The authors of this study used the old term "*Pneumocystis carinii*" instead of the preferred *Pneumocystis jiroveci*.)

Maronn LM, Corden T, Drolet BA. *Pneumocystis carinii* pneumonia in infant treated with oral steroids for hemangioma. *Arch Dermatol*. 2007; 143(9):1224-1225.

ALL-TRANS RETINOIC ACID AS A CAUSE OF RESPIRATORY FAILURE

A 78-year-old woman present-

ed with a 3-week history of easy bruising. Physical examination revealed hematomas on her arms, chest, abdomen, and legs. Lab studies revealed a very low hemoglobin, white blood cell count, and platelets. A bone marrow biopsy confirmed the diagnosis of acute promyelocytic leukemia. The patient was treated with daunorubicin, cytarabine, and all-trans retinoic acid (*Vesanoid*).

By day 9 of therapy, the woman complained of dyspnea, nausea, and vomiting. She was tachycardic and her baseline serum creatinine had risen from 0.7 to 1.8 mg/dL (normal, 0.6 to 1.4 mg/dL). A chest x-ray showed bilateral pulmonary infiltrates. This clinical picture led her physicians to suspect "all-trans retinoic acid syndrome," a distinct entity that has been recognized for a number of years. This syndrome requires the presence of at least 3 of the following symptoms: weight gain, fever, pulmonary infiltrates, respiratory distress, pleural or pericardial effusions, hypotension, and renal failure.

The all-trans retinoic acid was discontinued and the patient was treated with high-dose dexamethasone; she made an excellent recovery within 4 days. The patient was later treated with the same medications and achieved a complete remission of the acute leukemia. The authors point out that retreatment with this offending agent does not usually cause the same adverse event.

Ahmed Z, Shaikh MA, Raval A, Mehta JB, Byrd, RP Jr, Roy TM. All-trans retinoic acid syndrome: another cause of drug-induced respiratory failure. *South Med J*. 2007;100(9):899-902.

DRONABINOL-INDUCED GYNECOMASTIA

A 58-year-old man had an

"extensive gastrointestinal history" and was given dronabinol (*Marinol*) 5 mg daily for recurrent, severe nausea. Thirty days later, the gentleman noticed swelling in his right breast, but he did not report the problem for another 2 months. On examination, a breast mass was noted to be retroareolar, mobile, and tender to palpation. There was not any lymphadenopathy nor any other physical problems. The serum levels of testosterone, prolactin, and thyroxine were all within normal limits. Aspiration of the mass showed cellularity consistent with gynecomastia. The patient did have a history of gynecomastia in his contralateral breast 20 years prior to this episode following unilateral orchiectomy treatment for testicular cancer.

The authors state that there are no previous reports of gynecomastia with dronabinol but that there are conflicting reports in the literature of gynecomastia associated with marijuana use.

Allen RC, Wallace AM, Royce M. Marinol-induced gynecomastia: a case report. *Amer J Med*. 2007;120(10):e1.

NEUTROPHILIC DERMATITIS SEEN WITH BORTEZOMIB

A 49-year-old man was treated with bortezomib (*Velcade*) for multiple myeloma. He had already failed treatment with anakinra, dexamethasone, and thalidomide. He developed bilateral periorbital edema during the first course of therapy. When the second cycle of therapy was initiated, the gentleman suffered an increase in skin toxicity, which included angioedema and "asymptomatic, erythematous papules-plaques measuring up to 1 cm on his face, neck, and upper trunk." Skin biopsy demonstrated a dense neutrophilic, perivascular infiltrate with some

necrosis and leukocytoclastic vasculitis.

After discontinuing the bortezomib, the patient was sent to the intensive care unit (ICU) and treated with IV diphenhydramine and corticosteroids. He responded well to this therapy. It was decided that he should stay on the bortezomib, and before his third cycle, he was pretreated with oral prednisone 25 mg daily and did not have recurrence of the rash or facial edema.

The authors point out that this proteasome inhibitor has shown excellent results in the treatment of multiple myeloma; however, it does have a significant incidence of toxic dermatological effects. Patients must be warned about the possibility of severe rashes with this agent.

Paiva CM, Kurtis B, Mekki M, Newman MA, Singhal S, Lacouture ME. Neutrophilic dermatitis associated with bortezomib in a patient with multiple myeloma. *Ann Oncol.* 2007;18(10):1744-1745.

UNFAVORABLE SMELL WITH A SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRI)

A 17-year-old man presented with classic symptoms of major depressive disorder. He was very depressed, restless, irritable, and hopeless. He described sleep problems and was having trouble concentrating in school. His interpersonal functioning was problematic. He was started on citalopram 10 mg daily, which was increased to 20 mg daily after 10 days. Because there was no improvement by 4 weeks, the dose of citalopram was raised to 40 mg daily. By week 8, the patient was showing marked clinical and subjective improvement; however, the young man was complaining of an "unfavorable and intolerable smell" (meaning his olfactory senses/sense of smell

were affected) that began around week 7. By week 7 of therapy, it was decided that the citalopram should be tapered off. The patient reported that the smell disappeared soon after the taper was started.

Many adverse effects have been reported with the SSRIs. This problem with sense of smell appears to be a new and rare complaint.

Ghanizadeh A. Unfavorable smell with citalopram? *J Clin Psychopharmacol.* 2007;27(5):528-529.

ALOE VERA-INDUCED HEPATITIS

Aloe vera is commonly used in skin creams as an emollient or for minor burns. It is purported to have anti-inflammatory effects. This herbal product is also used orally for various claims, including diabetes, constipation, immunomodulation, and others. Because it is a herbal product, there is little scientific evidence that any of these claims are valid.

A 73-year-old woman was transferred to a tertiary medical center from her local community hospital for evaluation of possible acute cholecystitis. She complained of malaise, poor appetite, and nausea of several weeks' duration. She lost 1.8 kg. She finally went to the hospital when she developed jaundice. She also had dark urine and light-colored stools for 4 or 5 days. She reported that she was not taking any medications at home. She apparently had no prior medical history.

An extensive workup, including a liver biopsy, was performed and the diagnosis of active hepatitis was made. The patient had been asked more than once about her history of medication use, but it was not until a pharmacist specifically asked about "any herbal products" that the patient finally stated that she had been taking a capsule of aloe

vera every 2 or 3 days for almost 5 years. She used the 500 mg aloe vera leaf capsules to treat constipation. She had not had any of the product during the 2 hospital stays and further observation and supportive care led to a normalization of the liver function tests.

The authors searched the international literature and found 2 other reports of hepatitis caused by the oral ingestion of aloe vera. And 1 more lesson from this case is that we must be more diligent in medication history assessments. We have to ask about nonprescription as well as herbal drug use.

Bottenberg MM, Wall GC, Harvey RL, Habib S. Oral aloe vera-induced hepatitis. *Ann Pharmacother.* 2007;41(10):1740-1743.

PULMONARY SARCOIDOSIS ATTRIBUTED TO ETANERCEPT

A 40-year-old man had a significant history of severe, deforming psoriatic arthritis for many years. His foot, elbow, knee, and hand joints were seriously effected. He failed therapy with various nonsteroidal anti-inflammatory drugs, sulfasalazine, and methotrexate. He was then placed on etanercept (*Enbrel*) therapy 25 mg subcutaneously twice weekly. Etanercept is an antitumor necrosis factor-alpha blocker.

About 10 months after starting the etanercept therapy, the patient developed a slowly progressive onset of dyspnea on exertion, wheezing, and coughing. He also felt febrile at times. After suffering with these symptoms, he presented to his local hospital. Chest x-rays revealed bilateral interstitial changes in the upper lungs along with mediastinal widening. The pulmonary function tests showed impaired diffusing capacity with restriction. After testing for infectious processes and malignancy

proved negative, he underwent a lung biopsy that showed “non-caseating granulomas consistent with sarcoidosis.” The etanercept was discontinued and the patient showed improvement. He was then placed on prednisone 40 mg daily, which was tapered over several months. By 6 months, all symptoms resolved.

The authors point out that etanercept and similar agents have actually been used to treat sarcoidosis, but there have been recent reports that this agent can actually cause the same problem. The most common pulmonary effects seen with etanercept are respiratory infections.

Farah RE, Shay MD. Pulmonary sarcoidosis associated with etanercept therapy. *Pharmacotherapy*. 2007;27(10):1446-1448.

SERIOUS ADVERSE DRUG EVENTS REPORTED TO THE FOOD AND DRUG ADMINISTRATION (FDA)

Two of my Institute for Safe Medication Practices (ISMP) colleagues and a researcher from the Wake Forest University School of Medicine recently published an analysis of serious adverse drug events culled from the FDA’s Adverse Event Reporting System (AERS). These data showed that there were almost 35,000 adverse events with serious outcomes in 1998 and by 2005 that number increased to almost 90,000 events. That was a 2.6-fold increase over the 7-year period. Likewise, there were 5,519 deaths due to these adverse events in 1998 and by 2005 there were 15,107 deaths, a 2.7-fold increase. A total of 1,489 medications were identified as the

principal suspects in patient deaths, but just 20% of those agents accounted for over 87% of the fatalities.

This study is well worth distributing to department heads in your facility to help increase awareness of the dangers associated with medications commonly used throughout our health systems. We must continue to emphasize patient counseling to catch the early signs of suspected drug toxicities and it is vitally necessary that we continue to expand our medication monitoring programs.

Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Arch Intern Med*. 2007;167(16):1752-1759. ■

